

Stem Cells in Orthopedics: A Comprehensive Guide for the General Orthopedist

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Abstract

The use of biologic adjuvants in the treatment of operative and nonoperative orthopedic injuries continues to expand in concert with our understanding of the acute and chronic healing process of musculoskeletal injuries. Stem cell treatments in orthopedics are among the most commonly explored options, and have found varying levels of success in promoting osseous and soft tissue healing. Basic science and translational studies have demonstrated the potential for broad application of stem cells in the treatment of a growing number of musculoskeletal injuries. Emerging clinical studies have also provided promising results, although

the vast majority of studies have featured small sample sizes and limited duration of follow-up. In addition, a number of important questions remain regarding the clinical safety, treatment delivery, and overall efficacy of stem cell augmentation of injured tissue in orthopedics. The objective of the current review is to present a broad overview of the current state of stem cell treatments in orthopedic surgery, with an emphasis on soft tissue healing. This review of stem cell treatment covers the basic science behind biologic augmentation, advantages of the various stem cell sources, preclinical results, and current and future clinical applications.

B iologic use in orthopedics is a continuously evolving field that complements technical, anatomic, and biomechanical advancements in orthopedics. Biologic agents are receiving increasing attention for their use in augmenting healing of muscles, tendons, ligaments, and osseous structures. As biologic augmentation strategies become increasingly utilized in bony and soft-tissue injuries, research on stem cell use in orthopedics continues to increase. Stem cell-based therapies for the repair or regeneration of muscle and tendon represent a promising technology going forward for numerous diseases.¹

Stem cells by definition are undifferentiated cells that have 4 main characteristics: (1) mobilization during angiogenesis, (2) differentiation into specialized cell types, (3) proliferation and regeneration,

and (4) release of immune regulators and growth factors.² Mesenchymal stem cells (MSCs) have garnered the most attention in the field of surgery due to their ability to differentiate into the tissues of interest for the surgeon.³ This includes both bone marrow-derived mesenchymal stem cells (bm-MSCs) and adipose-derived mesenchymal stem cells (a-MSCs). These multipotent stem cells in adults originate from mesenchymal tissues, including bone marrow, tendon, adipose, and muscle tissue.⁴ They are attractive for clinical use because of their multipotent potential and relative ease of growth in culture.⁵ They also exert a paracrine effect to modulate and control inflammation, stimulate endogenous cell repair and proliferation, inhibit apoptosis, and improve blood flow through secretion of chemokines, cytokines, and growth factors.^{6,7}

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Questions exist regarding the best way to administer stem cells, whether systematic administration is possible for these cells to localize to the tissue in need, or more likely if direct application to the pathologic area is necessary.^{8,9} A number of sources, purification process, and modes of delivery are available, but the most effective means of preparation and administration are still under investigation. The goal of this review is to illustrate the current state of knowledge surrounding stem cell therapy in orthopedics with a focus on osteoarthritis, tendinopathy, articular cartilage, and enhancement of surgical procedures.

Important Considerations

Common stem cell isolates include embryonic, induced pluripotent, and mesenchymal formulations (**Table 1**). MSCs can be obtained from multiple sites, including but not limited to the adult bone marrow, adipose, muscular, or tendinous tissues, and their use has been highlighted in the study of numerous orthopedic and nonorthopedic pathologies over the course of the last decade. Research on the use of embryonic stem cells in medical therapy with human implications has received substantial attention, with many ethical concerns by those opposed, and the existence of a potential risk of malignant alterations.^{8,10} Amniotic-derived stem cells can be isolated from amniotic fluid, umbilical cord blood, or the placenta and thus do not harbor the same social constraints as the aforementioned embryonic cells; however, they do not harbor the same magnitude of multi-differentiation potential, either.⁴

Adult MSCs are more locally available and easy to obtain for treatment when compared with embryonic and fetal stem cells, and the former has

a lower immunogenicity, which allows allogeneic use.¹¹ Safety has been preliminarily demonstrated in use thus far; Centeno and colleagues¹² found no neoplastic tissue generation at the site of stem cell injection after 3 years postinjection for a cohort of patients who were treated with autologous bm-MSCs for various pathologies. Self-limited pain and swelling are the most commonly reported adverse events after use.¹³ However, long-term data are lacking in many instances to definitively suggest the absence of possible complications.

Basic Science

Stem cell research encompasses a wide range of rapidly developing treatment strategies that are applicable to virtually every field of medicine. In general, stem cells can be classified as embryonic stem cells (ESCs), induced pluripotent stem (iPS) cells, or adult-derived MSCs. ESCs are embryonic cells derived typically from fetal tissue, whereas iPS cells are dedifferentiated from adult tissue, thus avoiding many of the ethical and legal challenges imposed by research with ESCs. However, oncogenic and lingering politico-legal concerns with introducing dedifferentiated ESCs or iPS cells into healthy tissue necessitate the development, isolation, and expansion of multi- but not pluripotent stem cell lines.¹⁴ To date, the most advantageous and widely utilized from any perspective are MSCs, which can further differentiate into cartilage, tendon, muscle, and bony tissue.^{7,15,16}

MSCs are defined by their ability to demonstrate in vitro differentiation into osteoblasts, adipocytes, or chondroblasts, adhere to plastic, express CD105, CD73, and CD90, and not express CD43, CD23, CD14 or CD11b, CD79 or CD19, or HLA-DR.¹⁷ Porada and Almeida-Porada¹⁸ have outlined

Table 1. Advantages and Disadvantages of Stem Cells by Source

Stem Cell Type	Source	Advantages	Disadvantages
Embryonic stem cells	Embryonic tissue	Pluripotent to all 3 germ layers; mesoderm, endoderm, ectoderm	Oncogenic potential, allogenic rejection, ethical and legal constraints
Induced pluripotent stem cells	Adult somatic tissue transfected with embryonic transcription factors	Pluripotent, decreased ethical concerns due to adult source, no allogenic rejection	Oncogenic potential, modest induction yield
Mesenchymal stem cells	Multiple fetal and adult tissue (umbilical cord, umbilical blood, placenta, skin, bone marrow, blood vessels, adipose, synovium, periosteum, dental pulp)	Can differentiate into tissues of interest: bone, cartilage, and tendon; immunosuppressive allowing for allo- and xeno-transplantation	Limited differentiation capacity, modest yield from host tissue

6 reasons highlighting the advantages of MSCs: 1) ease of isolation, 2) high differentiation capabilities, 3) strong colony expansion without differentiation loss, 4) immunosuppression following transplantation, 5) powerful anti-inflammatory properties, and 6) their ability to localize to damaged tissue. The anti-inflammatory properties of MSCs are particularly important as they promote allo- and xenotransplantation from donor tissues.^{19,20} MSCs can be isolated from numerous sources, including but not limited to bone marrow, periosteum, adipocyte, and muscle.²¹⁻²³ Interestingly, the source tissue used to isolate MSCs can affect differentiation capabilities, colony size, and growth rate (**Table 2**).²⁴ Advantages of a-MSCs include high prevalence and ease of harvest; however, several animal studies have shown inferior results when compared to bm-MSCs.²⁵⁻²⁷ More research is needed to determine the ideal source material for MSCs, which will likely depend in part on the procedure for which they are employed.²⁷

Following harvesting, isolation, and expansion, MSC delivery methods for treatments typically consist of either cell-based or tissue engineering approaches. Cell-based techniques involve the injection of MSCs into damaged tissues. Purely cell-based therapy has shown success in limited clinical trials involving knee osteoarthritis, cartilage repair, and meniscal repair.²⁸⁻³⁰ However, additional studies with longer follow-up are required to validate these preliminary findings. Tissue engineering approaches involve the construction of a 3-dimensional scaffold seeded with MSCs that is later surgically implanted. While promising in theory, limited and often conflicting data exist regarding the efficacy of tissue-engineered MSC implantation.³¹⁻³² Suboptimal scaffold vascularity is a major limitation to scaffold design, which may be

alleviated in part with the advent of 3-dimensional printing and the ability to more precisely alter scaffold architecture.^{14,33} Additional limitations include ensuring MSC purity and differentiation potential following harvesting and expansion. At present, the use of tissue engineering with MSCs is promising but it remains a nascent technology with additional preclinical studies required to confirm implant efficacy and safety.

Clinical Entities

Osteoarthritis

MSC therapies have emerged as promising treatment strategies in the setting of early osteoarthritis (OA). In addition to their regenerative potential, MSCs demonstrate potent anti-inflammatory properties, increasing their attractiveness as biologic agents in the setting of OA.³⁴ Over the past decade, multiple human trials have been published demonstrating the efficacy of MSC injections into patients with OA.^{35,36} In a study evaluating a-MSC injection into elderly patients (age >65 years) with knee OA, Koh and colleagues²⁹ found that 88% demonstrated improved cartilage status at 2-year follow-up, while no patient underwent a total knee arthroplasty during this time period. In another study investigating patients with unicompartmental knee OA with varus alignment undergoing high tibial osteotomy and microfracture, Wong and colleagues³⁷ reported improved clinical, patient-reported, and magnetic resonance imaging (MRI)-based outcomes in a group receiving a preoperative MSC injection compared to a control group. Further, in a recent randomized control trial of patients with knee osteoarthritis, Vega and colleagues³⁸ reported improved cartilage and quality of life outcomes at 1 year following MSC injection compared to a control group receiving a hyaluronic

Table 2. Common Sources for Mesenchymal Stem Cells with Documented Tissue-Type Differentiation and Source Advantages

MSC Source	Differentiation Potential	Advantages
Bone marrow	Chondrocyte, ⁸⁷ muscle, ⁸⁸ osteoblast, ⁸⁹ cardiocyte, ⁹⁰ mesangial cell, ⁹¹ hepatocyte ⁹²	Highest differentiation potential
Adipose	Chondrocyte, ²³ muscle, ²³ osteoblast, ⁹³ stromal cell ⁹³	Easily accessible, higher colony formation compared to bone marrow derived cells ⁹⁴
Synovium	Adipocyte, ²² chondrocyte, ²² muscle, ²² osteoblast ²²	Applicable for cartilage and tendon healing
Periosteum	Chondrocyte, ²² osteoblast ²³	Applicable to fracture nonunion healing ⁹⁵

Abbreviation: MSC, mesenchymal stem cell.

Adapted from Mafi R, Hindocha S, Mafi P, Griffin M, Khan WS. Sources of adult mesenchymal stem cells applicable for musculoskeletal applications - a systematic review of the literature. *Open Orthop J*. 2011;5 Suppl 2:242-248.

acid injection. In addition to knee OA, studies have also reported improvement in ankle OA following MSC injection.³⁹ While promising, many of the preliminary clinical studies evaluating the efficacy of MSC therapies in the treatment of OA are hindered by small patient populations and short-term follow-up. Additional large-scale, randomized studies are required and many are ongoing presently in hopes of validating these preliminary findings.³⁶

Tendinopathy

The quality of repaired tissue in primary tendon-to-tendon and tendon-to-bone healing has long been a topic of great interest.⁴⁰ The healing potential of tendons is inferior to that of other bony and connective tissues,⁴¹ with tendon healing typically resulting in a biomechanically and histologically inferior structure to the native tissue.⁴² As such, this has been a particularly salient opportunity for stem cell use with hopes of recapitulating a more normal tendon or tendon enthesis following injury. In addition to the acute injury, there is great interest in the application of stem cells to chronic states of injury such as tendinopathy.

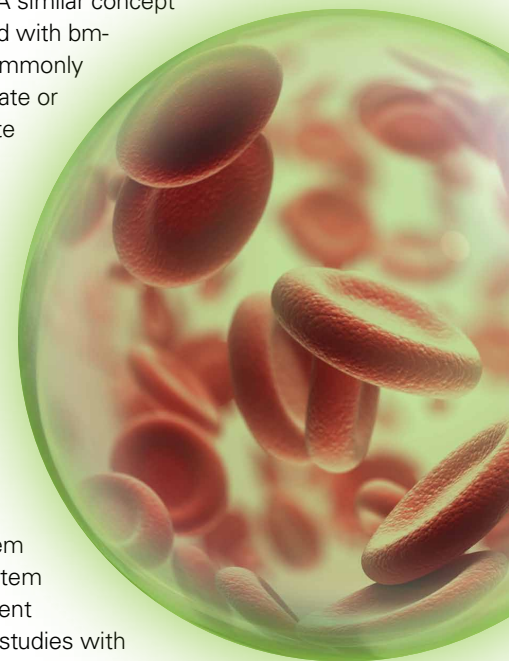
In equine models, the effect of autologous bm-MSCs treatment on tendinopathy of the superficial digital flexor tendon has been studied. Godwin and colleagues⁴³ evaluated 141 race horses with spontaneous superficial digital flexor tendinopathy treated in this manner, and reported a reinjury percentage in these treated horses of just 27.4%, which compared favorably to historical controls and alternative therapeutics. Machova Urdzikova and colleagues⁴⁴ injected MSCs at Achilles tendinopathy locations to augment nonoperative healing in 40 rats, and identified more native histological organization and improved vascularization in comparison to control rat specimens. Oshita and colleagues⁴⁵ reported histologic improvement of tendinopathy findings in 8 rats receiving a-MSCs at the location of induced Achilles tendinopathy that was significantly superior to a control cohort. Bm-MSCs were used by Yuksel and colleagues⁴⁶ in comparison with platelet-rich plasma (PRP) for treatment of Achilles tendon ruptures created surgically in rat models. They demonstrated successful effects with its use in terms of recovery for the tendon's histopathologic, immunohistochemical, and biomechanical properties, related to significantly greater levels of anti-inflammatory cytokines. However, these aforementioned findings have not been uniform across the literature—other authors have reported findings that MSC transplantation alone

did not repair Achilles tendon injury with such high levels of success.⁴⁷

Human treatment of tendinopathies with stem cells has been scarcely studied to date. Pascual-Garrido and colleagues⁴⁸ evaluated 8 patients with refractory patellar tendinopathy treated with injection of autologous bm-MSCs and reported successful results at 2- to 5-year follow-up, with significant improvements in patient-reported outcome measures for 100% of patients. Seven of 8 (87.5%) noted that they would undergo the procedure again.

Articular Cartilage Injury

Chondral injury is a particularly important subject given the limited potential of chondrocytes to replicate or migrate to the site of pathology.⁴⁹ Stem cell use in this setting assists with programmed growth factor release and alteration of the anatomic microenvironment to facilitate regeneration and repair of the chondral surface. Autologous stem cell use through microfracture provides a perforation into the bone marrow and a subsequent fibrin clot formation containing platelets, growth factors, vascular elements, and MSCs.⁵⁰ A similar concept to PRP is currently being explored with bm-MSCs. Isolated bm-MSCs are commonly referred to as bone marrow aspirate or bone marrow aspirate concentrate (BMAC). Commercially available systems are now available to aid in the harvesting and implementation of BMAC. One of the more promising avenues for BMAC implementation is in articular cartilage repair or regeneration due to chondrogenic potential of BMAC when used in isolation or when combined with microfracture, chondrocyte transfer, or collagen scaffolds.^{19,51} Synovial-derived stem cells as an additional source for stem cell use has demonstrated excellent chondrogenic potential in animal studies with full-thickness lesion healing and native-appearing cartilage histologically.⁵² Incorporation of a-MSCs into scaffolds for surgical implantation has demonstrated success in repairing full-thickness chondral defects with continuous joint surface and extracellular proteins, surface markers, and gene products similar to the native cartilage in animal models.^{53,54} In light of the promising basic science and animal



studies, clinical studies have begun to emerge.⁵⁵⁻⁵⁷

Fortier and colleagues⁵⁸ found MRI and histologic evidence of full-thickness chondral repair and increased integration with neighboring cartilage when BMAC was concurrently used at the time of microfracture in an equine model. Fortier and colleagues⁵⁸ also demonstrated greater healing in equine models with acute full-thickness cartilage defects treated by microfracture with MSCs than without delivery of MSCs. Kim and colleagues^{59,60} similarly reported superiority in clinical outcomes for patients with osteochondral lesions of the talus treated with marrow stimulation and MSC injection than by the former in isolation.

In humans, stem cell use for chondral repair has additionally proven promising. A systematic review of the literature suggested good to excellent overall outcomes for the treatment of moderate focal chondral defects with BMAC with or without scaffolds and microfracture with inclusion of 8 total publications.⁶¹ This review included Gobbi and colleagues,⁶² who prospectively treated 15 patients with a mean focal chondral defect size of 9.2 cm² about the knee. Use of BMAC covered with a collagen I/III matrix produced significant improvements in patient-reported outcome scores and MRI demonstrated complete hyaline-like cartilage coverage in 80%, with second-look arthroscopy demonstrating normal to nearly normal tissue. Gobbi and colleagues⁶² also found evidence for superiority of chondral defects treated with BMAC compared to matrix-induced autologous chondrocyte implantation (MACI) for patellofemoral lesions in 37 patients (MRI showed complete filling of defects in 81% of BMAC-treated patients vs 76% of MACI-treated patients).

Meniscal Repair

Clinical application of MSCs in the treatment of meniscal pathology is evolving as well. ASCs have been added to modify the biomechanical environment of avascular zone meniscal tears at the time of suture repair in a rabbit, and have demonstrated increased healing rates in small and larger lesions, although the effect lessens with delay in repair.⁶³ Angele and colleagues⁶⁴ treated meniscal defects in a rabbit model with scaffolds with bm-MSCs compared with empty scaffolds or control cohorts and found a higher proportion of menisci with healed meniscus-like fibrocartilage when MSCs were utilized.

In humans, Vangsness and colleagues³⁰ treated knees with partial medial meniscectomy with

allogeneic stem cells and reported an increase in meniscal volume and decrease in pain in those patients when compared to a cohort of knees treated with hyaluronic acid. Despite promising early results, additional clinical studies are necessary to determine the external validity and broad applicability of stem cell use in meniscal repair.

Rotator Cuff Repair

The number of local resident stem cells at the site of rotator cuff tear has been shown to decrease with tear size, chronicity, and degree of fatty infiltration, suggesting that those with the greatest need for a good reparative environment are those least equipped to heal.⁶⁵ The need for improvement in this domain is related to the still relatively high re-tear rate after rotator cuff repair despite improvements in instrumentation and surgical technique.⁶⁶ The native fibrocartilaginous transition zone between the humerus and the rotator cuff becomes a fibrovascular scar tissue after rupture and repair with poorer material properties than the native tissue.⁶⁷ Thus, a-MSCs have been evaluated in this setting to determine if the biomechanical and histological properties of the repair may improve.⁶⁸

In rat models, Valencia Mora and colleagues⁶⁸ reported on the application of a-MSCs in a rat rotator cuff repair model compared to an untreated group. They found no differences between those treated rats and those without a-MSCs use in terms of biomechanical properties of the tendon-to-bone healing, but those with stem cell use had less inflammation shown histologically (diminished presence of edema and neutrophils) at 2- and 4-week time points, which the authors suggested may lead to a more elastic repair and less scar at the bone-tendon healing site. Oh and colleagues¹ evaluated the use of a-MSCs in a rabbit subscapularis tear model, and reported significantly reduced fatty infiltration at the site of chronic rotator cuff tear after repair with its application at the repair site; while the load-to-failure was higher in those rabbits with ASCs administration, it was short of reaching statistical significance. Yokoya and colleagues⁶⁹ demonstrated regeneration of rotator cuff tendon-to-bone insertional site anatomy and in the belly of the cuff tendon in a rabbit model with MSCs applied at the operative site. However, Gulotta and colleagues⁷⁰ did not see the same improvement in their similar study in the rat model; these authors failed to see improvement in structure, strength, or composition of the tendinous attachment site

despite addition of MSCs.

Clinical studies on augmented rotator cuff repair have also found mixed results. MSCs for this purpose have been cultivated from arthroscopic bone marrow aspiration of the proximal humerus⁷¹ and subacromial bursa⁷² with successful and reproducibly high concentrations of stem cells. Hernigou and colleagues⁷³ found a significant improvement in rate of healing (87% intact cuffs vs 44% in the control group) and repair surface tendon integrity (via ultrasound and MRI) for patients at a minimum of 10 years after rotator cuff repair with MSC injection at the time of surgery. The authors found a direct correlation in these outcomes with the number of MSCs injected at the time of repair. Ellera Gomes and colleagues⁷⁴ injected bm-MSCs obtained from the iliac crest into the tendinous repair site in 14 consecutive patients with full-thickness rotator cuff tears treated by transosseous sutures via a mini-open approach. MRI demonstrated integrity of the repair site in all patients at more than 1-year follow-up.

Achilles Tendon Repair

The goal with stem cell use in Achilles repair is to accelerate the healing and rehabilitation. Several animal studies have demonstrated improved mechanical properties and collagen composition of tendon repairs augmented with stem cells, including Achilles tendon repair in a rat model. Adams and colleagues⁷⁵ compared suture alone (36 tendons) to suture plus stem cell concentrate injection (36 tendons) and stem cell loaded suture (36 tendons) in Achilles tendon repair with rat models. The suture-alone cohort had lower ultimate failure loads at 14 days after surgery, indicating biomechanical superiority with stem cell augmentation means. Transplantation of hypoxic MSCs at the time of Achilles tendon repair may be a promising option for superior biomechanical failure loads and histologic findings as per recent rat model findings by Huang and colleagues.⁷⁶ Yao and colleagues⁷⁷ demonstrated increased strength of suture repair for Achilles repair in rat models at early time points when using MSC-coated suture in comparison to standard suture, and suggested that the addition of stem cells may improve early mechanical properties during the tendon repair process. A-MSC addition to PRP has provided significantly increased tensile strength to rabbit models with Achilles tendon repair as well.⁷⁸

In evaluation of stem cell use for this purpose with humans, Stein and colleagues⁷⁹ reviewed

28 sports-related Achilles tendon ruptures in 27 patients treated with open repair and BMAC injection. At a mean follow-up of 29.7 months, the authors reported no re-ruptures, with 92% return to sport at 5.9 months, and excellent clinical outcomes. This small cohort study found no adverse outcomes related to the BMAC addition, and thus proposed further study of the efficacy of stem cell treatment for Achilles tendon repair.

Anterior Cruciate Ligament Reconstruction

Bm-MSCs genetically modified with bone morphogenetic protein 2 (BMP2) and basic fibroblast growth factor (bFGF) have shown great promise in improvement of the formation of mechanically sound tendon-bone interface in anterior cruciate ligament (ACL) reconstruction.⁸⁰ Similar to the other surgical procedures mentioned in this review, animal studies have successfully evaluated the augmentation of osteointegration of tendon to bone in the setting of ACL reconstruction. Jang and colleagues³ investigated the use of nonautologous transplantation of human umbilical cord blood-derived MSCs in a rabbit ACL reconstruction model. The authors demonstrated a lack of immune rejection, and enhanced tendon-bone healing with broad fibrocartilage formation at the transition zone (similar to the native ACL) and decreased femoral and tibial tunnel widening as compared to a control cohort at 12-weeks after surgery. In a rat model, Kanaya and colleagues⁸¹ reported improved histological scores and slight improvements in biomechanical integrity of partially transected rat ACLs treated with intra-articular MSC injection. Stem cell use in the form of suture-supporting scaffolds seeded with MSCs has been evaluated in a total ACL transection rabbit model; the authors of this report demonstrated total ACL regeneration in one-third of samples treated with this augmentation option, in comparison to complete failure in all suture and scaffold alone groups.⁸²

The use of autologous MSCs in ACL healing remains limited to preclinical research and small case series of patients. One human trial by Silva and colleagues⁸³ evaluated the graft-to-bone site of healing in ACL reconstruction for 20 patients who received an intraoperative infiltration of their graft with adult bm-MSCs. MRI and histologic analysis

Several animal studies have demonstrated improved mechanical properties and collagen composition of tendon repairs augmented with stem cells, including Achilles tendon repair in a rat model.

showed no difference in comparison to control groups, but the authors' conclusion proposed that the number of stem cells injected might have been too minimal to show a clinical effect.

Other Applications

Although outside the scope of this article, stem cells have demonstrated efficacy in the treatment of a number of osseous clinical entities. This includes the treatment of fracture nonunion, augmentation of spinal fusion, and assistance in the treatment of osteonecrosis.⁸⁴

Summary

As a scientific community, our understanding of the use of stem cells, their nuances, and their indications has expanded dramatically over the last several years. Stem cell treatment has particularly infiltrated the world of operative and nonoperative sports medicine, given in part the active patient population seeking greater levels of improvement.⁸⁵ Stem cell therapy offers a potentially effective therapy for a multitude of pathologies because of these cells' anti-inflammatory, immunoregulatory, angiogenic, and paracrine effects.⁸⁶ It thus remains a very dynamic option in the study of musculoskeletal tissue regeneration. While the potential exists for stem cell use in daily surgery practices, it is still premature to predict whether this can be expected.

The ideal stem cell sources (including allogeneic or autologous), preparation, cell number, timing, and means of application continue to be evaluated, as well as those advantageous pathologies that can benefit from the technology. In order to better answer these pertinent questions, we need to make sure we have a safe, economic, and ethically acceptable means for stem cell translational research efforts. More high-level studies with standardized protocols need to be performed. It is necessary to improve national and international collaboration in research, as well as collaboration with governing bodies, to attempt to further scientific advancement in this field of research.⁴⁹ Further study on embryonic stem cell use may be valuable as well, pending governmental approval. Finally, more dedicated research efforts must be placed on the utility of adjuncts with stem cell use, including PRP and scaffolds, which may increase protection, nutritional support, and mechanical stimulation of the administered stem cells.

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Continued on page 326

Continued from page 288

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This paper will be judged for the Resident Writer's Award.